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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,149	GEBAUER ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed December 15, 2003. Claims 1-44 were previously pending, with claims 13-44 withdrawn from consideration. Applicants cancelled claims 1-44 and added new claims 45-60.

2. Applicants' claim cancellations obviated the following: rejection of claims 1-4 under 35 U.S.C. 102(b) over Iizuka et al. and rejection of claims 5-7 under 35 U.S.C. 103(a) over Iizuka et al. and Scott et al.

3. Claims 45-60 are pending and will be examined.

Drawings

4. The drawings (corrected Fig. 11) were received on December 15, 2003. These drawings are accepted.

5. Figures 12 and 13 were objected to as presenting contradictory results. Applicants amended paragraphs on page 21 by changing the description of Fig. 8 to Fig. 12 and changing the description of Fig. 9 to Fig. 13. Applicants argue that the results presented in Fig. 12A and 12B are not contradictory, because "Figure 12 therefore illustrates 2 sets of experimental results depicting CAT transcript stability over time (and not translation efficiency or time optimization of translation reaction) and shows that "uncapped mRNA are...rapidly degradeld" (p. 21, lines 1 1-12).". However, the results presented in these two Figures are still contradictory, whether they correspond to translation efficiency or transcript stability. In addition, the following paragraph (page 21, lines 8 and 9), has a conclusory statement relating to the translational efficiency and based on these two figures. Therefore, whether the figure depicts transcript stability or translational efficiency of the different transcripts, the results at 60 and 90 minutes for Cap-pA and Cap transcripts are contradictory.

The objection is maintained.

1. The drawings are objected to because:

Figures 12A and 12 B seem to be showing results of similar experiments, i.e. time optimization of translation reaction. However, results for Cap and Cap-pA for the same time interval are contradictory: in Fig. 12A, at 60 minutes and 90 minutes, bars corresponding to Cap-pA are shorter than the ones corresponding to Cap alone, whereas the opposite is true in case of Figure 12B. There is no description in the specification of experiments which produced these results.

A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. No new matter should be introduced.

Oath/Declaration

6. The declaration was objected to because of non-initialed and non-dated alterations. Applicants did not address this issue in the response, the refore the objection is maintained

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Citizenship changes for Fatima Gebauer and Giovanna Bergamini are not initialed and not dated, and changes for Davide Corona are not dated.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 45-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of in vitro translation in Drosophila embryo cell extracts and incubation times of at least 90 minutes, does not reasonably provide enablement for in vitro translation using any other animal cell extract for incubation times shorter than 90 minutes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 45-60 are broadly drawn to methods of in vitro translation using animal cell extract under conditions which favor translation of mRNAs having both the 5' cap and the 3' poly(A) tail (Cap-pA) , in such a way that mRNAs having either poly(A) tail or only 5' cap are translated less efficiently. However, as will be further discussed, there is no support in the specification and prior art for the general method claimed. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification.

The specification provides no evidence that all of possible animal cell extracts will provide conditions favoring translation of Cap-pA mRNAs over Cap-only or poly(A) only mRNAs. Even though Applicants state that any animal cell extract can be used in the method (page 2, lines 23-28), Applicants also state the following: "It has been found, suprisingly, that by combining a dechorionation procedure that has been previously used for the study of chromatin assembly (Becker ef al., 1994) with homogenisation and centrifugation conditions used to study translation (Scott et al., 1979) a protocol results that allows the preparation of cell extract with greatly improved properties over conventionally known extracts for use in in vitro translation procedures." (page 2, lines 17-21). Therefore, since the improved method of cell extract preparation applies only to the Drosophila embryos, it is not clear whether any other animal cell extract will produce similar results, and Applicants did not provide such information.

Applicants provided data showing that Drosophila embryo cell extracts produce higher levels of translation products for Cap-pA mRNAs than for Cap-only and pA-only transcripts (Fig. 1 and 2). However, the results presented for HeLa cell extracts are contradictory. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention, since only one particular cell extract, obtained from Drosophila embryos, provided proper conditions to achieve the desired goal. Applicants state on page 8 that the incubation step needs to be performed for at least 90 minutes (page 8, lines 12-14).

Working Examples

The specification provides working examples for two translation systems: one obtained from Drosophila embryos (Examples 2 and 3) and one obtained from HeLa cells. The data provided by Example 3 supports the assertion that the Drosophila embryo cell extract produces the desired

synergistic effect in translating various mRNAs. However, Example 5, which describes the results of an assay in HeLa cell extracts does not provide support for the synergy effect. As can be seen by comparing Fig. 12A and 12B, the amounts of translation products for Cap-pA and Cap mRNAs after 60 minutes and 90 minutes are not in the same proportion: in Fig. 12A, the amount of Cap-pA is lower than the amount of Cap mRNA, while the reverse is shown for the same time periods in Fig. 12B. Further, as shown in Fig. 12A, after 90 minutes, the total amount of Cap-pA is only slightly higher that the sum of pA and Cap, so the amounts are additive within a probable experimental error. No working examples were provided for translational efficiencies of different mRNAs in Drosophila ovary cell extracts.

The unpredictability of the art and the state of the prior art

The efficiency of translation of mRNAs in in vitro translation methods is entirely unpredictable. For example, as shown by Iizuka et al. (Mol. Cell. Biol., vol. 14, pp. 7322-7330, 1994; cited in the IDS and in the previous office action), the efficiency of translation of the same exogenous mRNAs with different combinations of Cap and poly(A) structures varies from one system to another. As shown in Figure 4, in HeLa cell extracts the translation activity with Cap-pA mRNA was the same as with Cap-only mRNA, while in the rabit reticulocyte system the effect of Cap and poly(A) was additive within experimental error. The wheat germ extract showed moderate synergy effect, while the yeast cell extract had a very pronounced synergy effect.

Gallie (Genes and Dev., vol. 5, pp. 2108-2116, 1991) showed that while the synergy effect between the 5' cap and poly(A) tail can be observed by translating the mRNAs in vivo in CHO cells (Table 1 and 2), this effect is not reproducible in vitro in reticulocyte lysate (page 2111, sixth paragraph).

Munroe et al. (Mol. Cell. Biol., vol. 10, pp. 3441-3455, 1990), showed that in reticulocyte lysates, Cap-pA mRNAs exhibited better translational efficiency than either Cap-only or poly(A) only mRNAs, but the effect of adding the cap was not additive (Fig. 2A).

Therefore, prior art data point to the fact that the efficiency of translation of capped and uncapped mRNAs or mRNAs with or without poly(A) tails cannot be predicted a priori, but have to be evaluated on a system-by-system basis.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this method to all possible animal cell extracts. The term "animal cell extract" implies cell extracts from all possible animals (including humans), all possible stages of development of such animals, and all possible types of cells. Therefore, first one would have to obtain cell extracts from all possible cell types and stages of development of all possible animals. Then optimum conditions, including concentrations of all reaction mixture components, temperatures of reactions and time course of reactions would need to be determined in each of the cell extracts for translation of different mRNAs, of which there are potentially millions. Finally, the differences in translational efficiencies of Cap-pA, Cap-only and pA-only mRNAs would have to be determined in all of those cell extracts. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the translation of mRNAs in vitro depends upon numerous known and unknown parameters, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the in vitro translation of mRNAs in different cell-free systems (i.e encompassing a method in any cell type under any conditions). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of working examples and the negative teachings in the prior art balanced only against the high skill level in the

art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 45-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 45-60 are indefinite in claim 45. Claim 45 is indefinite because it is not clear how the sum of the amounts of proteins encoded by the mRNA templates with a 5' cap and poly(A) tail (= Cap-pA), 5' cap only (= Cap) and poly(A) tail only (= pA) are calculated.

1) First, it is not clear whether the reaction is performed with all of the above mRNAs in one tube, or whether there are three reaction tubes.

2) The total amount of produced protein depends on the total amount of mRNA in the reaction. Therefore, if there is no Cap mRNA and/or pA mRNA in the tube, there will be no protein expressed from those mRNAs. If the amounts of different mRNAs inputted are different, this will produce differences in the final amount of protein produced from each mRNA.

3) It is not clear whether the "ribonucleic acid template" refers to endogenous mRNA (i.e., the mRNA which will be present in the cell extract), or to exogenous mRNA, or both.

Claim Interpretation

12. As explained in the 35 U.S.C. 112, second paragraph, rejection above, claim 45 can be interpreted, if the reaction was performed in one tube, that in the absence of Cap mRNA and pA mRNA in the tube which has Cap-pA mRNA, the amount of protein produced from the Cap-pA mRNA will be greater than the sum of the amounts of proteins produced from Cap and pA mRNAs.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 45-47 and 57-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Iizuka et al. (Mol. Cell Biol., vol. 14, pp. 7322-7330, 1994; cited in the IDS and in the previous office action), as evidenced by Hussain et al. (Gene, vol. 46, pp. 13-23, 1986; cited in the IDS).

Regarding claim 45, Iizuka et al. teach in vitro translation of a ribonucleic acid having both a 5' cap and a 3' poly A tail (capped and polyadenylated luciferase mRNA) by incubating a cell extract of HeLa cells or rabbit reticulocytes (= multicellular eucaryote cells) with the ribonucleic acid under conditions such that translation of the RNA template to produce its encoded protein occurs (page 7324, paragraphs 7 and 8; Fig. 1; Fig. 4). In the rabbit reticulocyte system, the amount of the protein produced from RNA template which has a 5' cap and a poly A tail was 3.7 units. Since there was no cap-only or poly(A) tail-only mRNA in this tube, the total amount produced from the capped and polyadenylated transcript in that tube is higher than the sum of the cap-only and poly(A) tail-only transcripts in that tube (Fig. 4). The same result was obtained for HeLa cells (Fig. 4).

Regarding claim 46, Iizuka et al. teach mammalian cell extracts: rabbit reticulocyte cell extract and HeLa cell extract (page 7324, paragraph 7; Fig. 4).

Regarding claim 47, Iizuka et al. teach human cell extract, HeLa cell extract (page 7324, paragraphs 7; Fig. 4).

Regarding claim 57, Iizuka et al. teach the reaction conditions given in Hussain et al. (page 7324, 7th paragraph). Hussain et al. teach the presence of creatine phosphate, creatine kinase,

potassium and magnesium acetate (= potassium and magnesium salts), spermidine, amino acids, DTT (= a reducing agent) and tRNA (page 15, last paragraph; page 17, first paragraph). Therefore Iizuka et al. teach the limitations of claim 57.

Regarding claims 58 and 59, Iizuka et al. teach the reaction conditions given in Hussain et al. (page 7324, 7th paragraph). Hussain et al. teach incubation temperature of 20 degrees Celsius (page 17, first paragraph). Since 20 degrees Celsius is between 18 and 37 degrees Celsius, and about 25 degrees Celsius, Iizuka et al. teach the limitations of claims 58 and 59.

Regarding claim 60, Iizuka et al. teach the reaction conditions given in Hussain et al. (page 7324, 7th paragraph). Hussain et al. teach incubation time of 120 minutes (page 17, first paragraph). Since 120 minutes is at least 90 minutes, Iizuka et al. teach the limitation of claim 60.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iizuka et al. (Mol. Cell Biol., vol. 14, pp. 7322-7330, 1994; cited in the IDS and in the previous office action) and Scott et al. (Biochemistry, vol. 18, pp. 1588-1594, 1979; cited in the IDS and in the previous office action).

A) Claim 48 is drawn to the method of claim 45 wherein the cell extract is an insect cell extract, claim 49 is drawn to the method of claim 48 wherein the cell extract is Drosophila cell extract, claim 50 is drawn to the method of claim 49 wherein the cell extract is Drosophila embryo cell extract.

B) Iizuka et al. do not teach insect cell extract, Drosophila cell extract or Drosophila embryo cell extract.

C) Scott et al. teach in vitro translation of proteins in cell extracts obtained from Drosophila cell culture and from Drosophila embryos (page 1589, paragraphs 5-12; Fig. 2; Fig. 5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used Drosophila cell lysates and Drosophila embryo cell lysates of Scott et al. in the method of Iizuka et al. The motivation to do so, provided by Scott et al., would have been that Drosophila lysates synthesized high molecular weight proteins in greater abundance than other cell-free systems and the lysates were easy to prepare (page 1590, the last paragraph, continued on page 1591; page 1593, the last paragraph).

17. No references were found teaching or suggesting claims 51-56, but they are rejected for reasons given above.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
February 25, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER